1. Document ID: US 6165471 A

L4: Entry 1 of 4

File: USPT

Dec 26, 2000

US-PAT-NO: 6165471
DOCUMENT-IDENTIFIER: US 6165471 A
TITLE: Homogeneous human papillomavirus capsomere containing compositions, methods for
manufacture, and use thereof as diagnostic, prophylactic or therapeutic agents
DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 424/186.1; 424/192.1, 424/199.1, 435/235.1, 435/320.1, 435/69.1, 435/69.3,
536/23.4, 536/23.72

APPL-NO: 9/ 109036
DATE FILED: July 2, 1998

PARENT-CASE:
This application claims priority under 35 U.S.C. .sctn..sctn.119 and/or 365 to Ser. No.
60/051,678 filed in the United States on Jul. 3, 1997; the entire content of which is herby
incorporated by reference.

IN: Garcea; Robert L., Suzich; JoAnn A., McCarthy; Michael P., Rose; Robert C.

AB: The present invention relates to stable HPV capsomeres which express at least one
virus-neutralizing conformational epitope of a native HPV L1 protein which are substantially
incapable of assembly into virus-like particles. These capsomeres, because of their smaller
size, and immunogenic properties are well suited for use in HPV vaccines and as diagnostic
agents. Moreover, because of their smaller size (relative to VLPs), these stable capsomeres
may be easily purified and should result in HPV vaccines of enhanced homogeneity.

L4: Entry 1 of 4

File: USPT

Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165471 A
TITLE: Homogeneous human papillomavirus capsomere containing compositions, methods for
manufacture, and use thereof as diagnostic, prophylactic or therapeutic agents

DEPR:
In this regard, it has been reported that in the 3.8 .ANG. structure of the SV40 virus, that the
C-terminal domain of the VP1 protein is involved in the formation of intra-capsomeric bonds which
stabilize the capsid, by extending across the space between capsomeres and forming part of the
extended .beta.-sheet of the neighboring capsomeric L1 protein. However, the requirement of
disulfide bonds for this interaction was not resolved in the crystal structure because of
disorder in this portion of the molecule (Liddington et al, Nature, 354:278-284 (1991)). Also, it
was previously reported that 15 .ANG. strands connecting capsomeres can be seen, at low
resolution, in the cryoelectron microscopic reconstruction of the BPV structure (Baker et al,
Biophys J., 60:1445-1456 (1991); Belnap et al, J. Mol. Biol., 259:249-263 (1996)); and also in
negatively-stained HPV virions (Yabe et al, Virology, 227:13-23 (1997)). These results suggested
that linker arms may stabilize papillomavirudae capsids. [However, it is noted that these
references did not provide any information concerning what specific residues or role of other
factors which potentially could have affected PV capsid formation and stability.]

2. Document ID: US 5849478 A

L4: Entry 2 of 4

File: USPT

Dec 15, 1998

US-PAT-NO: 5849478
DOCUMENT-IDENTIFIER: US 5849478 A
TITLE: Blocked-polymerase polynucleotide immunoassay method and kit
DATE-ISSUED: December 15, 1998

US-CL-CURRENT: 435/6; 435/7.1, 435/810, 435/91.1, 435/91.2, 436/501, 536/22.1, 536/23.1,
536/24.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33

APPL-NO: 7/ 996793
DATE FILED: December 24, 1992

PARENT-CASE:
This application is a continuation-in-part of U.S. patent application Ser. No. 07/508,259, filed
Apr. 11, 1990, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No.
07/272,648 filed Nov. 17, 1988, now abandoned which in turn is a continuation-in-part of U.S.
patent application Ser. No. 06/897,142 filed Aug. 14, 1986, now abandoned.

IN: Cashman; Daniel P.

AB: An immunoassay method for detecting an analyte in a liquid sample is disclosed.
The method includes first contacting the sample with a polynucleotide assay reagent composed
of a analyte and an attached polynucleotide containing an initiation region adjacent the
site of attachment to the analyte. The sample is reacted with a polymerase and nucleotide
triphosphates, to determine the amount of immunocomplex formed between the analyte and the
analyte under conditions effective to copy the polynucleotide only if its initiation region
is not blocked. The assay mixture is then assayed for the presence of phosphate or
pyrophosphate. An immunoassay kit for detecting an analyte in a liquid sample is also
disclosed.

L4: Entry 2 of 4

File: USPT

Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849478 A
TITLE: Blocked-polymerase polynucleotide immunoassay method and kit

DEPR:
The outer capsid of SV40 virus is composed of repeating units of the major surface protein VP1
which makes up 70% of the viron protein. SV40 virus DNA (Life

Technologies,Inc.) is transfected
into CV1 cells (Life Technologies, Inc.) by calcium phosphate method of Graham. From lytic foci
of the initial transfection a virus is plaque purified and then confluent CV1 cell cultures are
infected with 5 plaque forming units per cell to produce a virus rich supernatant fluid. Virus is
purified according to the method of Barban.

3. Document ID: US 5118627 A

L4: Entry 3 of 4
File: USPT
Jun 2, 1992

US-PAT-NO: 5118627
DOCUMENT-IDENTIFIER: US 5118627 A
TITLE: Papova virus construction
DATE-ISSUED: June 2, 1992

US-CL-CURRENT: 435/466; 435/320.1, 435/69.3

APPL-NO: 6/ 584132
DATE FILED: February 27, 1984

IN: Browne; Jeffrey K.

AB: A microbial shuttle vector is disclosed which is independently replicative in
bacterial cells and mammalian cells and includes in its DNA sequence bacterial plasmid
sequences allowing selection and replication in bacterial cells, an SV40 viral origin of
replication, and either an SV40 functional "early gene" promoter and functional "early gene"
terminator or an SV40 functional "late gene" promoter and functional "late gene" terminator,
the vector having a unique restriction endonuclease enzyme recognition site between the
promoter and terminator for insertion of an exogenous gene. The presence of restriction
endonuclease enzyme recognition sites facilitative of insertion of a viral functional "late
gene" into the "early gene" promoter/terminator vector in a single step allows for
conversion of the shuttle vector into a lytic vector of an exogenous gene. The presence of
restriction endonuclease enzyme recognition sites facilitative of insertion of a viral
functional "late gene" into the "late gene" promoter/terminator vector in a single step
allows for conversion of the shuttle vector into a lytic vector.

L4: Entry 3 of 4
File: USPT
Jun 2, 1992

DOCUMENT-IDENTIFIER: US 5118627 A
TITLE: Papova virus construction

BSPR:
In Liu, DNA, 1, supra, an SV40 vector for the direct expression of exogenous genes was
constructed by eliminating SV40 genome sequences between HindIII (1493) [6 nucleotides 5' to the
initiation codon for the gene coding for the major SV40 late protein, VP1, which is essential in
capsid formation] and BamHI (2533) [50 nucleotides 5' to the termination codon for that gene]. A
unique EcoRI restriction endonuclease enzyme recognition site was introduced into the SV40 genome
at the HindIII terminus to allow the SV40 fragment to be cloned into pBR322 and amplified. A
BamHI/EcoRI exogenous gene sequence, e.g., HBsAg, is inserted into the SV40 fragment in place of
the deleted VP1 sequence and the SV40-HBsAg fragment cloned into a pBR322 derivative and
amplified. Cleavage with BamHI and self-ligation results in a recombinant virus plasmid vector,
therefore, lacking only the coding region of VP1 and containing the whole protein coding region
for T antigen. When the recombinant SV40/hepatitis B virus DNA was introduced into permissive
monkey cells by DNA transfection in the presence of helper virus (tsA28), which supplies the
capsid protein normally expressed by the deleted VP1, HBsAg was synthesized at a level comparable
to that of VP1.

4. Document ID: US 4968627 A

L4: Entry 4 of 4
File: USPT
Nov 6, 1990

US-PAT-NO: 4968627
DOCUMENT-IDENTIFIER: US 4968627 A
TITLE: DNA fragments coding an immunogen peptide liable of inducing in vivo synthesis of
anti-poliovirus antibodies
DATE-ISSUED: November 6, 1990

US-CL-CURRENT: 435/320.1; 424/185.1, 424/217.1, 435/91.41, 536/23.72

APPL-NO: 6/ 886754
DATE FILED: July 15, 1986

PARENT-CASE:
This application is a continuation of application Ser. No. 464,175, filed 2/7/83, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	82 02013	February 8, 1982

IN: Girard; Marc, van der Werf; Sylvie

AB: DNA fragment capable of coding for an immunogenic peptide capable of inducing in
vivo antibody reacting with anti-poliovirus. It possesses up to the order of 1.2 kilobase
pairs and contains a nucleotide sequence coding for the poliovirus VP1 protein.

L4: Entry 4 of 4
File: USPT
Nov 6, 1990

DOCUMENT-IDENTIFIER: US 4968627 A

TITLE: DNA fragments coding an immunogen peptide liable of inducing in vivo synthesis of
anti-poliovirus antibodies

DEPR:
It is particularly the case of the use of the virus SV40 as vector. In this case, the late viral
promoter is used and the VP1 fragment of the poliovirus is inserted in the place of all or part
of the region coding for the tardive proteins of SV40 (VP1 or VP2). In this way substituted SV40
DNas are constructed in which the sequences coding for the capsid proteins of this virus are
replaced by the sequence coding for the VP1 protein of the poliovirus. Thus, the insertion of the
fragment HaeII-PstI of poliovirus described in paragraph 3 above, in place of the tardive
fragment Hae II-PstI of SV40 (nucleotides from 767 to 1923) results, after phase restoration of
the two sequences at the level of the HaeII site, in creating a chimerical gene possessing the
VP1 sequence of the poliovirus directly linked behind and to the N terminal portion of the
sequence coding for the VP2 protein of SV40.

1. Document ID: US 6235521 B1

L6: Entry 1 of 33
File: USPT
May 22, 2001

US-PAT-NO: 6235521
DOCUMENT-IDENTIFIER: US 6235521 B1
TITLE: Phage bonded to a nuclear location signal
DATE-ISSUED: May 22, 2001

US-CL-CURRENT: 435/320.1; 424/93.2, 424/93.6, 435/456

APPL-NO: 9/ 242131
DATE FILED: September 10, 1999

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	8-227787	August 9, 1996

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/JP96/03861	December 27, 1996	WO98/06828	Feb 19, 1998	Sep 10, 1999	Sep 10, 1999

IN: Nakanishi; Mahito, Nagoshi; Emi, Akuta; Teruo, Takeda; Katsuo, Hasegawa; Mamoru

AB: A .lambda. phage with a nuclear localization signal has been obtained by
constructing a vector capable of expressing a fused protein between a gpD protein
constituting the head of a .lambda. phage and a nuclear localization signal sequence,
transforming Escherichia coli with this vector, and propagating a mutant .lambda. phage
which cannot express the gpD protein in E. coli in this transformant. It has been confirmed
that the resulting .lambda. phage is capable of packaging .lambda. phage DNAs of 80% and
100% genome sizes. After further confirming that the nuclear localization signal exposed on
the outside of the head of this phage, this phage has been microinjected into cells to
analyze its nuclear localization activity. Thus, it has been clarified that this phage has a
nuclear localization activity.

L6: Entry 1 of 33
File: USPT
May 22, 2001

DOCUMENT-IDENTIFIER: US 6235521 B1
TITLE: Phage bonded to a nuclear location signal

BSPR:
It has been suggested that, on the viruses that infect animals such as adenovirus and SV40, the
nuclear localization signals exist in their capsid proteins, and they function to actively
translocate their DNA at the early stage of infection (Urs. F. Greber and Harumi Kasamatsu,
Trends in Cell Biology 6: 189-195 (1996)). It has been also suggested that the SV40 particle with
its diameter of 45 nm invade the nucleus in the form of virion (K. Hummeler et al., J. Virol. 6:
87-93 (1970)). Furthermore, MS-2 phage is reported to have a transport system in which exogenous
substances are enveloped by the capsid (International Application published in Japan No.
Hei-508168). However, any transport system using virus particles, which is capable of using long
chain DNA and translocating the DNA into the nucleus, has not been reported.

2. Document ID: US 6204059 B1

L6: Entry 2 of 33
File: USPT
Mar 20, 2001

US-PAT-NO: 6204059
DOCUMENT-IDENTIFIER: US 6204059 B1
TITLE: AAV capsid vehicles for molecular transfer
DATE-ISSUED: March 20, 2001

US-CL-CURRENT: 435/456; 435/320.1, 435/440, 514/44

APPL-NO: 8/ 268430
DATE FILED: June 30, 1994

IN: Samulski; Richard Jude, Ferrari; Forrest K.

AB: The invention relates to the production of AAV capsids which may be used to

transfer native or heterologous molecules into appropriate host cells. The capsid proteins
can be expressed from a recombinant virus, expression vector, or from a cell line that has
stably integrated the AAV capsid genes or coding sequences. The invention further provides
for the production of AAV capsids in vitro from the AAV capsid proteins and the construction
of packaged capsids in vitro. The invention further provides for the production of AAV
capsids that have been genetically engineered to express heterologous epitopes of clinically
important antigens to elicit an immune response.

L6: Entry 2 of 33

File: USPT

Mar 20, 2001

DOCUMENT-IDENTIFIER: US 6204059 B1
TITLE: AAV capsid vehicles for molecular transfer

DEPR:
In a specific embodiment, adenovirus is used as the recombinant virus. Deletion strains of
adenovirus can accommodate the insertion of the heterologous material, i.e., the AAV capsid
coding region, into non-essential regions of the adenovirus such as E1 or E3. Infection of
adenovirus into a complementing host cell line, such as the 293 line, will allow the expression
of the AAV capsid proteins and the subsequent assembly of these into the capsid vehicle.
Heterologous promoters for the capsid genes may be used, including but not limited to CMV, pGK,
beta actin, RSV, SV40, and transthyretin liver specific promoter. Host cells may include AS49,
HeLa, Cos-1, KB and Vero.

3. Document ID: US 6165471 A

L6: Entry 3 of 33

File: USPT

Dec 26, 2000

US-PAT-NO: 6165471
DOCUMENT-IDENTIFIER: US 6165471 A
TITLE: Homogeneous human papillomavirus capsomere containing compositions, methods for
manufacture, and use thereof as diagnostic, prophylactic or therapeutic agents
DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 424/186.1; 424/192.1, 424/199.1, 435/235.1, 435/320.1, 435/69.1, 435/69.3,
536/23.4, 536/23.72

APPL-NO: 9/ 109036
DATE FILED: July 2, 1998

PARENT-CASE:
This application claims priority under 35 U.S.C. .sctn..sctn.119 and/or 365 to Ser. No.
60/051,678 filed in the United States on Jul. 3, 1997; the entire content of which is herby
incorporated by reference.

IN: Garcea; Robert L., Suzich; JoAnn A., McCarthy; Michael P., Rose; Robert C.

AB: The present invention relates to stable HPV capsomeres which express at least one
virus-neutralizing conformational epitope of a native HPV L1 protein which are substantially
incapable of assembly into virus-like particles. These capsomeres, because of their smaller
size, and immunogenic properties are well suited for use in HPV vaccines and as diagnostic
agents. Moreover, because of their smaller size (relative to VLPs), these stable capsomeres
may be easily purified and should result in HPV vaccines of enhanced homogeneity.

L6: Entry 3 of 33

File: USPT

Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165471 A
TITLE: Homogeneous human papillomavirus capsomere containing compositions, methods for
manufacture, and use thereof as diagnostic, prophylactic or therapeutic agents

DEPR:
In this regard, it has been reported that in the 3.8 .ANG. structure of the SV40 virus, that the
C-terminal domain of the VP1 protein is involved in the formation of intra-capsomeric bonds which
stabilize the capsid, by extending across the space between capsomeres and forming part of the
extended .beta.-sheet of the neighboring capsomeric L1 protein. However, the requirement of
disulfide bonds for this interaction was not resolved in the crystal structure because of
disorder in this portion of the molecule (Liddington et al, Nature, 354:278-284 (1991)). Also, it
was previously reported that 15 .ANG. strands connecting capsomeres can be seen, at low
resolution, in the cryoelectron microscopic reconstruction of the BPV structure (Baker et al,
Biophys J., 60:1445-1456 (1991); Belnap et al, J. Mol. Biol., 259:249-263 (1996)); and also in
negatively-stained HPV virions (Yabe et al, Virology, 227:13-23 (1997)). These results suggested
that linker arms may stabilize papillomavirudae capsids. [However, it is noted that these
references did not provide any information concerning what specific residues or role of other
factors which potentially could have affected PV capsid formation and stability.]

4. Document ID: US 6132732 A

L6: Entry 4 of 33

File: USPT

Oct 17, 2000

US-PAT-NO: 6132732
DOCUMENT-IDENTIFIER: US 6132732 A
TITLE: Parvovirus capsids
DATE-ISSUED: October 17, 2000

US-CL-CURRENT: 424/233.1; 435/235.1, 435/5, 435/69.3

APPL-NO: 8/ 407939
DATE FILED: March 21, 1995

PARENT-CASE:
This application is a division of application Ser. No. 07/612,672, filed Nov. 14, 1990, U.S. Pat.
No. 5,508,186, which is a continuation-in-part of application Ser. No. 07/270,098, filed Nov. 14,
1988, abandoned, which are hereby incorporated in their entirety by reference.

IN: Young; Neal S., Kajigaya; Sachiko, Takashi; Shimada

AB: The present invention relates to a method of producing non-infections parvovirus
capsids and to diagnostic assays and vaccines utilizing same. The invention further relates
to recombinant baculoviruses encoding parvovirus structural proteins and host cells infected
therewith. The invention also relates to a method of packaging and delivering genetic
information utilizing the noninfectious capsids.

L6: Entry 4 of 33
File: USPT
Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6132732 A
TITLE: Parvovirus capsids

DEPR:
In a most preferred embodiment, CHO cells deficient in dihydrofolate reductase (DHFR) are
cotransfected with: i) a recombinant DNA molecule comprising an expression vector and a DNA
sequence encoding the two B19 parvovirus capsid proteins driven by the strong single B19
promoter, and ii) a human DHFR minigene driven by the SV40 early promoter enhancer unit.
Transformants bearing the DHFR+ phenotype are selected by growing the cells in a medium lacking
nucleosides; colonies are screened by RNA Northern analysis for expression of B19 genes.
Coamplification of the integrated B19 capsid-encoding sequence and the DHFR sequence can be
accomplished by treating the cells with increasing concentrations of methotrexate;
coamplification results in detectable levels of protein expression.

5. Document ID: US 6090608 A

L6: Entry 5 of 33
File: USPT
Jul 18, 2000

US-PAT-NO: 6090608
DOCUMENT-IDENTIFIER: US 6090608 A
TITLE: SV-40 derived DNA constructs comprising exogenous DNA sequences
DATE-ISSUED: July 18, 2000

US-CL-CURRENT: 435/235.1; 435/320.1, 435/325, 435/455, 536/23.5

APPL-NO: 8/ 737047
DATE FILED: January 15, 1997

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
IL
109558
May 4, 1994

PCT-DATA:
APPL-NO
DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/US95/05595
May 4, 1995
WO95/30762
Nov 16, 1995
Jan 15, 1997
Jan 15, 1997

IN: Oppenheim; Ariella, Dalyot; Nava, Ben-Nun-Shaul; Orly, Rund; Deborah, Sandalon;
Ziv, Chajek-Shaul; Toba, Metzger; Shulamit

AB: The invention relates to DNA constructs comprising an exogenous DNA sequence
encoding a therapeutic protein product or itself a therapeutic product, DNA sequences
derived from SV40 for replication and packaging of said construct into pseudovirions, and a
DNA sequence encoding one or more regulatory elements sufficient for the expression of said
therapeutic protein in a mammalian cell operatively linked thereto. The therapeutic product
integrated into the DNA constructs of the invention can be a protein selected from the group
consisting of enzymes, receptors, structural proteins, regulatory proteins and hormones. Of
particular interest are .beta.-globin, P-glycoprotein and apolipoprotein A-I. Specific DNA
constructs are plasmids pSO6.beta.-9, pSO6.beta.-1, pSO41, pSM1, and pSAIc. The invention
also relates to SV40 pseudovirions containing a DNA construct according to the invention,
which are capable of infecting and being expressed in mammalian cells. Also within the scope
of the invention are transduced mammalian cells having integrated into their genome a DNA
construct according to the invention, said cells being capable of expressing the therapeutic
protein product. The invention also relates to a method for in vivo and ex vivo treatment of
an individual suffering from an acquired or hereditary pathological disorder, in which a
therapeutic product is not made by said individual, or is made in abnormally low amounts or
in a defective form or is normally made in physiological amounts to be increased by
employing the DNA construct, pseudovirions or transduced cells of the invention.

L6: Entry 5 of 33
File: USPT
Jul 18, 2000

DOCUMENT-IDENTIFIER: US 6090608 A
TITLE: SV-40 derived DNA constructs comprising exogenous DNA sequences

DEPR:
Thus, the vectors that have been developed, in accordance with the present invention, carry the
SV40 origin of replication (ori) and packaging signal (ses) to facilitate replication and

packaging of plasmid in the COS cells. The SV40 capsid proteins are supplied in trans by a helper
SV40 DNA, cotransfected into the COS cells.

DEPR:
As mentioned above, encapsidation (packaging) of a plasmid to be used for expression in erythroid
cells is best carried out in COS cells which constitutively express the SV40 T-antigen. Further,
while the vector SO6.beta.-9 carries the SV40 ori and ses sequences to facilitate replication and
packaging of the plasmid in the COS cells, SV40 capsid proteins must be provided and these are
supplied in trans by a helper SV40 DNA which is co-transfected with the plasmid into the COS
cells. Thus, the encapsidation procedure is briefly as follows:

6. Document ID: US 6043077 A

L6: Entry 6 of 33
File: USPT
Mar 28, 2000

US-PAT-NO: 6043077
DOCUMENT-IDENTIFIER: US 6043077 A
TITLE: Hepatitis C virus ribozymes
DATE-ISSUED: March 28, 2000

US-CL-CURRENT: 435/236; 435/320.1, 435/325, 435/363, 435/366, 435/375, 435/6, 435/91.31,
536/23.1, 536/23.2, 536/24.1, 536/24.5

APPL-NO: 8/ 954210
DATE FILED: October 20, 1997

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATION This application is a continuation-in-part of U.S.
application Ser. No. 08/608,862, filed Feb. 29, 1996 now abandoned; and claims priority under 35
U.S.C. .sctn..sctn. 119/365 from pending PCT Application No. PCT/US97/03304, filed Feb. 27, 1997,
which applications are incorporated by reference in their entirety.

IN: Barber; Jack R., Welch; Peter J., Tritz; Richard, Yei; SoonPin, Yu; Mang

AB: This invention provides ribozymes useful to treat or prevent Hepatitis C Virus
("HCV") infection or disease in an organism or subject, as well as methods of treating an
HCV infection or disease. Reagents such as vectors, host cells, DNA molecules coding for
these ribozymes useful in methods of treatment and prevention of HCV infection or disease
are also provided.

L6: Entry 6 of 33
File: USPT
Mar 28, 2000

DOCUMENT-IDENTIFIER: US 6043077 A
TITLE: Hepatitis C virus ribozymes

DEPR:
Construction of several expression vectors is described herein (FIG. 9). The HCV reporter plasmid
pPur-HCV (FIG. 9B) is constructed as follows: HCV sequences containing the 5'UTR and capsid
coding region are synthesized directly from RNA that is extracted from an HCV-positive patient
serum sample. The purified viral RNA is then reverse transcribed and PCR amplified with the
following primers: sense (starting at 5' end of 5' UTR) 5'-GCCAGCCCCC TGATGGGG-3' (Sequence ID
No. 6) and antisense (starting at 3' end of capsid coding region) 5'-CACCTGATAA GCGGAAGC-3'
(Sequence ID No. 7). The resulting blunt-end DNA is then ligated into plasmid pPur (Clontech,
Palo Alto, Calif.; FIG. 9A) that has been digested with XbaI and blunt-ended with Klenow DNA
polymerase. The HCV reporter retroviral vector pLNL-Pur-HCV (FIG. 9D) is constructed by purifying
the 2065 bp PvuII/XbaI fragment from pPur-HCV, which contains the SV40 early promoter, the
puromycin resistance coding region and the HCV 5'UTR and capsid sequences. The fragment is
blunt-ended with Klenow and cloned into plasmid pLNL6 (Bender et al., J. Virol. 61:1639-1646,
1987; FIG. 9C) that has been digested with HindIII and blunt-ended with Klenow. Both resulting
HCV reporter plasmids will then produce an RNA transcript, via SV40 early promoter, that contains
the HCV 5' UTR and capsid sequences on the same RNA transcript as the coding region for puromycin
resistance. Each HCV ribozyme is expressed on a separate retroviral vector (pLNT-Rz) via the
tRNA.sup.val pol III promoter. Active HCV ribozymes will cleave the Pur-HCV RNA, resulting in a
cell sensitive to puromycin.

7. Document ID: US 6017734 A

L6: Entry 7 of 33
File: USPT
Jan 25, 2000

US-PAT-NO: 6017734
DOCUMENT-IDENTIFIER: US 6017734 A
TITLE: Unique nucleotide and amino acid sequence and uses thereof
DATE-ISSUED: January 25, 2000

US-CL-CURRENT: 435/69.7; 435/320.1, 435/348, 435/365, 435/91.4, 536/23.1, 536/23.72, 536/24.1

APPL-NO: 8/ 792832
DATE FILED: January 30, 1997

PARENT-CASE:
The present application is a continuation-in-part of U.S. patent application Ser. No. 08/678,435
filed Jul. 3, 1996, abandoned, which claims the priority date of U.S. Provisional patent
application Ser. No. 60/000,955 filed Jul. 7, 1995. The entire text of each of the
above-referenced disclosures is specifically incorporated by reference herein without disclaimer.

IN: Summers; Max D., Braunagel; Sharon C., Hong; Tao

AB: Provided are hydrophobic targeting sequences, which may serve to target
heterologous proteins to a variety of cellular membranes. In particular, the structural
components of the nuclear envelope, or those components which become nucleus-associated, may
be targeted with the sequences provided. Also provided are methods of

targeting heterologous
proteins to particular membranes, and the use of these targeted proteins in therapeutic,
diagnostic and insecticidal applications.

L6: Entry 7 of 33

File: USPT

Jan 25, 2000

DOCUMENT-IDENTIFIER: US 6017734 A
TITLE: Unique nucleotide and amino acid sequence and uses thereof

DETL:
particles haemorrhagic disease virus capsid Nagesha et al. 1995 protein haemorrhagic disease
virus structural Marin et al. 1995 protein VP60 hemorrhagic disease virus casid Laurent et al.
1994 protein 55 kDa 2P protein Prasad et al. 1996 55-kilodalton zona pellucida protein Prasad et
al. 1995 Na.sup.+ /glucose cotransporter protein Smith et al. 1992 papillomavirus L1 Breitburd et
al. 1995 papillomavirus L2 Breitburd et al. 1995 prolactin receptor Cahoreau et al. 1992
prolactin receptor Cahoreau et al. 1994 skeletal muscle protein phosphatase 1 Cohen and Berndt
1991 UDP-GlcNac:a3-D-mannoside b-1, Sarkar 1994 2-N-acetylglucosaminyltransferase I catalytic
domain rabies virus: ERA strain - G protein Fu et al. 1993 glycoprotein Prehaud et al. 1989
Tuchiya et al. 1992 nucleoprotein Fu et al. 1991 M1; M2 Prehaud et al. 1990 N, M1, M2 antigens
Prehaud et al. 1992 rat: 1, 25 dihydroxy vitamin D.sub.3 receptor Ross et al. 1991 a subunit of g
protein (a.sub.i-1, a.sub.0, a.sub.5) Lebierque et al. 1992 a.sub.il protein Jones et al. 1993
androgen receptor Xie et al. 1992 androgen receptor Kallio et al. 1994 androgen receptors Kallio
et al. 1994 anion exchanger AE2 He et al. 1993 annexin 5 Takehara et al. 1994 bacterial
dehydrase-domain mutant Williams et al. 1996 rat fatty acid synthase polyhydroxyalkanoate
synthase brain Type II calmodulin - dependent Takeuchi-Suzuki et al. 1992 protein kinase - a
subunit CTP:phosphocholine Luche et al. 1993 cytidylyltransferase calcineurin A Perrino et al.
1992 calmodulin-dependent protein Kitani et al. 1995 kinase IV cytochrome P450 Asseffa et al.
1989 D.sub.2 dopamine receptors Woodcock et al. 1995 D.sub.2 dopamine receptor isoform Boundy et
al. 1996 D.sub.3 dopamine receptors Woodcock et al. 1995 10-formyltetrahydrofolate Krupenko et
al. 1995 dehydrogenase a subunits FTase farnyl transferase Moomaw et al. 1995 b subunits FTase
farnyl transferase Moomaw et al. 1995 GABA.sub.A receptor subtypes Im et al. 1994 gastric
H,K-ATPase a & b subunit Klaassen et al. 1993 glucocorticoid receptor Alnemri et al. 1991
glutamate receptor subunits GluR-B, Keinanen et al. 1994 GluR-D glycoprotein hormone a-subunit
Delahaye et al. 1996 guanylate cyclase Buechler et al. 1995 hepatic microsomal epoxide
Lacourciere et al. 1993 hydrolase hormone-sensitive lipase Holm et al. 1994 intrinsic factor
Gordon et al. 1992 JAK2 (type 2 Janus tyrosine kinase) Duhe & Farrar 1995 protein-tyrosine kinase
liver Ybi glutathione S-transferase Hsieh et al. 1989 liver CTP: phosphocholine cytidylyl
MacDonald and Kent 1993 transferase liver phenylalanine hydroxylase Gibbs et al. 1993 lysyl
hydroxylase Armstrong & Last 1995 m3 muscarinic acetylcholine receptor Vasudevan et al. 1995
a.sub.1 -microglobulin Akerstrom et al. 1995 a.sub.1 -microglobulin-bikunin Bratt & Akerstrom
1995 multifunctional animal fatty acid Joshi & Smith 1993 synthaes muscarinic acetylcholine
receptor Vasudevan et al. 1992 subtype m3 Na, K-ATPase a2, a3, B1 isoforms Blanco et al. 1993
a4b2 neuronal nicotinic cholinergic Wang & Abood 1996 receptor neuronal nitric oxide synthase
Richards & Marletta 1994 nitric oxide synthase Harteneck et al. 1994 nuclear pore protein p62
Bailer et al. 1995 p53 Fuchs et al. 1995 p70.sup.56K and p85.sup.56K kinases Kozma et al. 1993
pancreatic cholesteral esterase di Persio et al. 1992 pancreatic lithostathine Bimmler et al.
1995 papillomavirus L1 Breitburd et al. 1995 papillomavirus L2 Breitburd et al. 1995 peroxisomal
Acyl-CoA oxidase Chu et al. 1994 phospholipase C-g1 Horstman et al. 1995 prostatic acid
phosphatase Vihko et al. 1993 protein kinase C-d McGlynn et al. 1992 protein kinase C-x McGlynn
et al. 1992 protein kinase C-y Fiebich et al. 1990 ram p25 Suzuki et al. 1992 recombinant liver
carnitine Johnson et al. 1995 palmitoyltransferase II renal Na/P.sub.i -cotransport (NaP.sub.i
-2) Fucentese et al. 1995 skeletal muscle chloride channel Astill et al. 1996 ClC-1 skeletal
muscle phosphorylase kinase Lee et al. 1992 skeletal muscle phorylase kinase g Lee et al. 1992
subunit soluble, mutant G-protein a subunit Jones et al. 1993 substance receptor Schreurs et al.
1995 urate oxidase Alvares et al. 1992 receptor tyrosine kinase p180 Guy et al. 1994 respiratory
syncytial virus F Wathen et al. 1989 glycoprotein retroviral gag precursors Tobin et al. 1995
rhesus rotavirus: VP5(1) Dunn et al. 1995 VP8 Dunn et al. 1995 ricin B Ferrini et al. 1995
Rickettsia rickettsii rOmpA protein Sumner et al. 1995 Rift valley fever virus: cDNA-complete
Takahara et al. 1990 envelope glycoproteins G1 and G2 Schmaljohn et al. 1989 Rinderpest
hemagglutinin and fusion Bassiri et al. 1993 proteins Rinderpest virus (kabete O strain) Ismail
et al. 1994 N protein Rinderpest virus nucleocapsid gene Kamata et al. 1993 rodent Na,K-ATPase
DeTomaso et al. 1993 rotavirus: bovine VP1 Cohen et al. 1989 bovine VP2, VP6 Labbe et al. 1991
bovine VP6, VP7 Sabara et al. 1991 (Group C) - VP6 Tosser et al. 1992 (Group A) - VP2 Tosser et
al. 1992 human adult diarrheal VP6 Mackow et al. 1993 like particles Zeng et al. 1996 murine VP1;
VP2; NS53; VP4; VP7; Dharakul et al. 1991 VP6; NS28; NS35 porcine VP4 gene product Nishikawa et
al. 1989 rat (IDIR) group B, VP6 Lindsay et al. 1993 rhesus outer capsid protein VP4 Mackow et
al. 1990 simian major capsid antigen Estes et al. 1987 simian nonstructural glycoprotein Au et
al. 1989 simian SAII protein Estes et al. 1987 simian SAII - VP7 McGonigal et al. 1992 simian VP3
Mattson & Estes 1992 strain RF VP2 Zeng et al. 1994 VP2 Labbe et al. 1991 VP3 Liu et al. 1992 VP6
protein Sabara et al. 1991 VP7 protein Sabara et al. 1991 Rous sarcoma virus v-Src Park et al.
1992 Rubella virus: E2 glycoprotein Seto et al. 1995 p110 polyprotein precursor Oker-Blom et al.
1995 spike proteins Oker-Blom et al. 1990 SIV Pr56.sup.gag Yamshchikov et al. 1995 SV40 capsid
proteins VP1 Kosukegawa et al. 1996 VP2 Kosukegawa et al. 1996 VP3 Kosukegawa et al. 1996 Ayola
et al. 1993 Saccharo myces cerevisiae Kex2p Germain et al. 1992 endoprotease Sarcophaga peregrina
sarcotoxin 1A Yamada et al. 1990 Schistosoma mansoni sarcotoxima Felleisen et al. 1990 protein
Sm32 scorpion: a anti-insect neurotoxin (LqhaIT) Chejanovsky et al. 1995 Buthus eupeus
insectotoxin-1 Carbonell et al. 1988 Buthus occitaus tunetanus a-toxin Bouhaouah-Zahar et al.
1996 secreted alkaline phosphatase Davis et al. 1993 Semliki forest virus: capsid protein Favre
et al. 1993 membrane protein subunits Barth et al. 1995 Sendai Virus: fusion protein Sato et al.
1993 hemagglutinin-neuraminidase Sato et al. 1993 sheep choriogonadotropin- Johnson et al. 1995

immunoglobulin.G heavy-chain silk moth chorion chromosomal gene Iatrou et al. 1989 product simian
immunodeficiency virus Hu et al. 1992 gp160 simian rotavirus SA11 VP2, VP4, Crawford et al. 1994
VP6, VP7 simian sarcoma virus v-sis platlet Giese et al. 1989 derived growth factor B simian
virus: 40 large and small T antigen Lanford et al. 1988 Murphy et al. 1988 40 large T antigen
Hoss et al. 1990 40 T-antigen Shearer et al. 1993 40 T and t antigen Murphy et al. 1988 40 small
t antigen Jeang et al. 1987 gag, pro, pol Sommerfelt et al. 1993 Sindbis virus: 26S: 6 structural
proteins Oker-Blom et al. 1989 nsP1, nsP2, nsP3, nsP4 Buzan and Schlesinger 1992 nsP3 Lastarza et
al. 1994 snowshoe hare bunyavirus Urakawa et al. 1988 nucleoprotein and non structural protein
NS-S soluble class I MHC heavy chain Wang et al. 1996 protein stromelysin Peakman et al. 1992
swine fever virus: glycoprotein E2 Hulst et al. 1994 protein E2 Ruggli et al. 1995 TMV movement
protein Atkins et al. 1991 Tenebrio molitor desiccation stre Graham et al. 1996 gene Theileria
parva sporozoite surface Nene et al. 1995 protein NS1-p67 Thogoto virus glycoprotein Jones et al.
1995 tobacco mosaic virus movement Atkins et al. 1991 protein tomato golden mosaic virus AL1
Fontes et al. 1992 Tonga virus NS1 Qu et al. 1993 Toronto virus capsid protein TV24 Leite et al.
1996 Torpedo californica Radic et al. 1992 acetylcholinesterase transmissible gastroenteritis
virus S Godet et al. 1991 gene transmissible gastroenteritis virus Tuboly et al. 1994 spike
protein Trypanosoma: brucei surface transferrin Ligtenberg et al. 1994 transferrin-binding
protein complex Chaudhri et al. 1994 congolense variable surface Urakawa et al. 1995 glycoprotein
(mVSGs) cruzi flagellar repetitive antigen Duarte dos Santos et al. 1992 vivax antigen Masake et
al. 1995 turnip yellow mosaic virus 69K Seron et al. 1996 movement protein v-cath proteinase
Slack et al. 1995 Vaccinia surface antigen Morikawa & Ueda 1993 Vaccinia virus Ag.sup.35 Mohandas
et al. 1994 varicella-zoster virus origin-binding Webster et al. 1995 protein vesicular
stomatitis virus: glycoprotein Bailey et al. 1989 matrix protein Li et al. 1993 L protein Mathur
et al. 1996 M protein Li et al. 1993 N protein Ahamad et al. 1993 viral haemorrhagic septicaemia
Lecocq-Zhonneux et al. 1994 glycoprotein Vibrio harveyi: b-galactosidase McIntosh & Grasela 1994
luciferase McIntosh & Grasela 1994 Xenopus: bone morphogenetic protein (xBMP)-2 Hazama et al.
1995 (xBMP)-4 Hazama et al. 1995 (xBMP)-7 Hazama et al. 1995

8. Document ID: US 6001371 A

L6: Entry 8 of 33

File: USPT

Dec 14, 1999

US-PAT-NO: 6001371
DOCUMENT-IDENTIFIER: US 6001371 A
TITLE: Parvovirus capsids
DATE-ISSUED: December 14, 1999

US-CL-CURRENT: 424/233.1; 424/489

APPL-NO: 8/ 462464
DATE FILED: June 5, 1995

PARENT-CASE:
This application is a division of application Ser. No. 07/612,672, filed Nov. 14, 1990, U.S. Pat.
No. 5,508,186, which is a continuation-in-part of application Ser. No. 07/270,098, filed Nov. 14,
1988, abandoned, which are hereby incorporated in their entirety by reference.

IN: Young; Neal S., Kajigaya; Sachiko, Shimada; Takashi

AB: The present invention relates to a method of producing non-infections parvovirus
capsids and to diagnostic assays and vaccines utilizing same. The invention further relates
to recombinant baculoviruses encoding parvovirus structural proteins and host cells infected
therewith. The invention also relates to a method of packaging and delivering genetic
information utilizing the noninfectious capsids.

L6: Entry 8 of 33

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001371 A
TITLE: Parvovirus capsids

DEPR:
In a most preferred embodiment, CHO cells deficient in dihydrofolate reductase (DHFR) are
cotransfected with: i) a recombinant DNA molecule comprising an expression vector and a DNA
sequence encoding the two B19 parvovirus capsid proteins driven by the strong single B19
promoter, and ii) a human DHFR minigene driven by the SV40 early promoter enhancer unit.
Transformants bearing the DHFR+ phenotype are selected by growing the cells in a medium lacking
nucleosides; colonies are screened by RNA Northern analysis for expression of B19 genes.
Coamplification of the integrated B19 capsid-encoding sequence and the DHFR sequence can be
accomplished by treating the cells with increasing concentrations of methotrexate;
coamplification results in detectable levels of protein expression.

9. Document ID: US 5916563 A

L6: Entry 9 of 33

File: USPT

Jun 29, 1999

US-PAT-NO: 5916563
DOCUMENT-IDENTIFIER: US 5916563 A
TITLE: Parvovirus protein presenting capsids
DATE-ISSUED: June 29, 1999

US-CL-CURRENT: 424/192.1; 424/233.1, 435/174, 435/235.1, 435/317.1, 530/350

APPL-NO: 8/ 253539
DATE FILED: June 3, 1994

PARENT-CASE:
This application is a divisional application of Ser. No. 07/843,067, filed Mar. 2, 1992, now
abandoned, which is, in turn, a continuation-in-part of application Ser. No. 07/612,672, filed

Nov. 14, 1990, now U.S. Pat. No. 5,508,186, which is, in turn, a continuation-in-part of application Ser. No. 07/270,098, filed Nov. 14, 1988, now abandoned, all of which are hereby incorporated in their entirety by reference.

IN: Young; Neal S., Kajigaya; Sachiko, Takashi; Shimada

AB: The present invention relates to a parvovirus protein presenting capsid. Protein presenting capsid can be made by substituting nonparvovirus proteins, such as antigenic epitopes, ligands, enzymes, or peptide sequences, for the unique region of the parvovirus minor structural protein (e.g. VP1). Small regions of VP2 can also be replaced. Normal VP2 can be added to enhance capsid formation.

L6: Entry 9 of 33

File: USPT

Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916563 A
TITLE: Parvovirus protein presenting capsids

DEPR:
In a most preferred embodiment, CHO cells deficient in dihydrofolate reductase (DHFR) are cotransfected with: i) a recombinant DNA molecule comprising an expression vector and a DNA sequence encoding the two B19 parvovirus capsid proteins driven by the strong single B19 promoter, and ii) a human DHFR minigene driven by the SV40 early promoter enhancer unit.
Transformants bearing the DHFR+ phenotype are selected by growing the cells in a medium lacking nucleosides; colonies are screened by RNA Northern analysis for expression of B19 genes.
Coamplification of the integrated B19 capsid-encoding sequence and the DHFR sequence can be accomplished by treating the cells with increasing concentrations of methotrexate;
coamplification results in detectable levels of protein expression.

10. Document ID: US 5863541 A

L6: Entry 10 of 33

File: USPT

Jan 26, 1999

US-PAT-NO: 5863541
DOCUMENT-IDENTIFIER: US 5863541 A
TITLE: AAV capsid vehicles for molecular transfer
DATE-ISSUED: January 26, 1999

US-CL-CURRENT: 424/192.1; 424/204.1, 424/234.1, 435/235.1, 435/320.1

APPL-NO: 8/ 472594
DATE FILED: June 6, 1995

PARENT-CASE:
This is a continuation of application Ser. No. 08/268,430 filed Jun. 30, 1994.

IN: Samulski; Richard Jude, Ferrari; Forrest K.

AB: The invention relates to the production of AAV capsids which may be used to transfer native or heterologous molecules into appropriate host cells. The capsid proteins can be expressed from a recombinant virus, expression vector, or from a cell line that has stably integrated the AAV capsid genes or coding sequences. The invention further provides for the production of AAV capsids in vitro from the AAV capsid proteins and the construction of packaged capsids in vitro. The invention further provides for the production of AAV capsids that have been genetically engineered to express heterologous epitopes of clinically important antigens to elicit an immune response.

L6: Entry 10 of 33

File: USPT

Jan 26, 1999

DOCUMENT-IDENTIFIER: US 5863541 A
TITLE: AAV capsid vehicles for molecular transfer

DEPR:
In a specific embodiment, adenovirus is used as the recombinant virus. Deletion strains of adenovirus can accommodate the insertion of the heterologous material, i.e., the AAV capsid coding region, into non-essential regions of the adenovirus such as E1 or E3. Infection of adenovirus into a complementing host cell line, such as the 293 line, will allow the expression of the AAV capsid proteins and the subsequent assembly of these into the capsid vehicle.
Heterologous promoters for the capsid genes may be used, including but not limited to CMV, pGK, beta actin, RSV, SV40, and transthyretin liver specific promoter. Host cells may include AS49, HeLa, Cos-1, KB and Vero.

11. Document ID: US 5849478 A

L6: Entry 11 of 33

File: USPT

Dec 15, 1998

US-PAT-NO: 5849478
DOCUMENT-IDENTIFIER: US 5849478 A
TITLE: Blocked-polymerase polynucleotide immunoassay method and kit
DATE-ISSUED: December 15, 1998

US-CL-CURRENT: 435/6; 435/7.1, 435/810, 435/91.1, 435/91.2, 436/501, 536/22.1, 536/23.1, 536/24.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33

APPL-NO: 7/ 996793
DATE FILED: December 24, 1992

PARENT-CASE:
This application is a continuation-in-part of U.S. patent application Ser. No. 07/508,259, filed Apr. 11, 1990, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/272,648 filed Nov. 17, 1988, now abandoned which in turn is a continuation-in-part of U.S. patent application Ser. No. 06/897,142 filed Aug. 14, 1986, now abandoned.

IN: Cashman; Daniel P.

AB: An immunoassay method for detecting an analyte in a liquid sample is disclosed.
The method includes first contacting the sample with a polynucleotide assay reagent composed
of a analyte and an attached polynucleotide containing an initiation region adjacent the
site of attachment to the analyte. The sample is reacted with a polymerase and nucleotide
triphosphates, to determine the amount of immunocomplex formed between the analyte and the
analyte under conditions effective to copy the polynucleotide only if its initiation region
is not blocked. The assay mixture is then assayed for the presence of phosphate or
pyrophosphate. An immunoassay kit for detecting an analyte in a liquid sample is also
disclosed.

L6: Entry 11 of 33
File: USPT
Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849478 A
TITLE: Blocked-polymerase polynucleotide immunoassay method and kit

DEPR:
The outer capsid of SV40 virus is composed of repeating units of the major surface protein VP1
which makes up 70% of the viron protein. SV40 virus DNA (Life Technologies,Inc.) is transfected
into CV1 cells (Life Technologies, Inc.) by calcium phosphate method of Graham. From lytic foci
of the initial transfection a virus is plaque purified and then confluent CV1 cell cultures are
infected with 5 plaque forming units per cell to produce a virus rich supernatant fluid. Virus is
purified according to the method of Barban.

12. Document ID: US 5827647 A

L6: Entry 12 of 33
File: USPT
Oct 27, 1998

US-PAT-NO: 5827647
DOCUMENT-IDENTIFIER: US 5827647 A
TITLE: Parvovirus capsids
DATE-ISSUED: October 27, 1998

US-CL-CURRENT: 435/5; 435/235.1

APPL-NO: 8/ 463332
DATE FILED: June 5, 1995

PARENT-CASE:
This application is a divisional application of Ser. No. 07/612,672, filed Nov. 14, 1990, now
U.S. Pat. No. 5,508,186, which is a continuation-in-part of application Ser. No. 07/270,098,
filed Nov. 14, 1988, now abandoned, all of which are hereby incorporated in their entirety by
reference.

IN: Young; Neal S., Kajigaya; Sachiko, Shimada; Takashi

AB: The present invention relates to a method of producing non-infectious-parvovirus
capsids and to diagnostic assays and vaccines utilizing same. The invention further relates
to recombinant baculoviruses encoding parvovirus structural proteins and host cells infected
therewith. The invention also relates to a method of packaging and delivering genetic
information utilizing the noninfectious capsids.

L6: Entry 12 of 33
File: USPT
Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827647 A
TITLE: Parvovirus capsids

DEPR:
In a most preferred embodiment, CHO cells deficient in dihydrofolate reductase (DHFR) are
cotransfected with: i) a recombinant DNA molecule comprising an expression vector and a DNA
sequence encoding the two B19 parvovirus capsid proteins driven by the strong single B19
promoter, and ii) a human DHFR minigene driven by the SV40 early promoter enhancer unit.
Transformants bearing the DHFR+phenotype are selected by growing the cells in a medium lacking
nucleosides; colonies are screened by RNA Northern analysis for expression of B19 genes.
Coamplification of the integrated B19 capsid-encoding sequence and the DHFR sequence can be
accomplished by treating the cells with increasing concentrations of methotrexate;
coamplification results in detectable levels of protein expression.

13. Document ID: US 5741683 A

L6: Entry 13 of 33
File: USPT
Apr 21, 1998

US-PAT-NO: 5741683
DOCUMENT-IDENTIFIER: US 5741683 A
TITLE: In vitro packaging of adeno-associated virus DNA
DATE-ISSUED: April 21, 1998

US-CL-CURRENT: 435/457; 435/235.1, 435/325, 435/366, 435/5

APPL-NO: 8/ 477538
DATE FILED: June 7, 1995

IN: Zhou; Xiaohuai, Muzyczka; Nicholas, Zolotukhin; Sergei, Ni; Tiehua

AB: A method for in vitro packaging of adeno-associated viral particles is described.
The procedure involves the preparation of cell-free extracts containing all the essential
components for packaging. Homogeneous purified substrate DNA for packaging may be prepared
separately. The in vitro packaged AAV particles are useful in transduction of mammalian
cells and for gene therapy in animals. In one described method, the DNA packaged into AAV
particles is not limited by the size constraints characteristic of in vivo packaged AAV

particles.

L6: Entry 13 of 33

File: USPT

Apr 21, 1998

DOCUMENT-IDENTIFIER: US 5741683 A
TITLE: In vitro packaging of adeno-associated virus DNA

BSPR:
The use of AAV as a viral transduction vector was first demonstrated by Hermonat and Muzyczka
(Proc. Natl Acad. Sci. 81:6466-6470 1984). The AAV capsid gene was deleted between map positions
52 and 92 to make the vector d152-91, and the bacterial neomycin resistance gene under the
control of the SV40 early promoter was inserted. A d152-91/neo virus stock was obtained by
transfecting the recombinant plasmid into human cells that had been infected with adenovirus. The
missing capsid proteins were supplied by co-transfecting with a plasmid containing wild type cap
genes. This approach generated d151-91/neo virus stocks that contained up to 10.sup.6 infectious
units/ml (Hermonat et al. 1984 J. Virol., 51:329-333). The transduction frequency of these stocks
was approximately the same as the integration frequency for wild type virus, 0.5%-5.0% (Laughlin
et al. 1986 J. Virol. 60:515-524 (1986); Handa et al. 1977 Virology 82:84-92). Other AAV vectors
containing the AAV TR sequences and varying amounts of non-repeated AAV sequences have been
demonstrated to be capable of efficiently transducing foreign DNA into human cells (McLaughlin et
al. 1988 J. Virol. 62: 1963-1973; Samulski et al. 1987 J. Virol. 61:3096-3101; Samulski et al.
1989 J. Virol. 63:3822-3828).

particles is not limited by the size constraints characteristic of in vivo packaged AAV
particles.

L6: Entry 14 of 33

File: USPT

Nov 18, 1997

DOCUMENT-IDENTIFIER: US 5688676 A
TITLE: In vitro packaging of adeno-associated virus DNA

BSPR:
The use of AAV as a viral transduction vector was first demonstrated by Hermonat and Muzyczka
(Proc. Natl Acad. Sci. 81:6466-6470 1984). The AAV capsid gene was deleted between map positions
52 and 92 to make the vector dl52-91, and the bacterial neomycin resistance gene under the
control of the SV40 early promoter was inserted. A dl52-91/neo virus stock was obtained by
transfecting the recombinant plasmid into human cells that had been infected with adenovirus. The
missing capsid proteins were supplied by co-transfecting with a plasmid containing wild type cap
genes. This approach generated dl51-91/neo virus stocks that contained up to 10.sup.6 infectious
units/ml (Hermonat et al. 1984 J. Virol., 51:329-333). The transduction frequency of these stocks
was approximately the same as the integration frequency for wild type virus, 0.5%-5.0% (Laughlin
et al. 1986 J. Virol. 60:515-524 (1986); Handa et al. 1977 Virology 82:84-92). Other AAV vectors
containing the AAV TR sequences and varying amounts of non-repeated AAV sequences have been
demonstrated to be capable of efficiently transducing foreign DNA into human cells (McLaughlin et
al. 1988 J. Virol. 62:1963-1973; Samulski et al. 1987 J. Virol. 61:3096-3101; Samulski et al.
1989 J. Virol. 63:3822-3828).

14. Document ID: US 5688676 A

L6: Entry 14 of 33

File: USPT

Nov 18, 1997

US-PAT-NO: 5688676
DOCUMENT-IDENTIFIER: US 5688676 A
TITLE: In vitro packaging of adeno-associated virus DNA
DATE-ISSUED: November 18, 1997

US-CL-CURRENT: 435/457; 435/320.1, 435/456

APPL-NO: 8/ 477511
DATE FILED: June 7, 1995

IN: Zhou; Xiaohuai, Muzyczka; Nicholas, Zolotukhin; Sergei, Ni; Tiehua

AB: A method for in vitro packaging of adeno-associated viral particles is described.
The procedure involves the preparation of cell-free extracts containing all the essential
components for packaging. Homogeneous purified substrate DNA for packaging may be prepared
separately. The in vitro packaged AAV particles are useful in transduction of mammalian
cells and for gene therapy in animals. In one described method, the DNA packaged into AAV

15. Document ID: US 5688675 A

L6: Entry 15 of 33

File: USPT

Nov 18, 1997

US-PAT-NO: 5688675
DOCUMENT-IDENTIFIER: US 5688675 A
TITLE: In vitro packaging of adeno-associated virus DNA
DATE-ISSUED: November 18, 1997

US-CL-CURRENT: 435/457; 435/320.1, 435/456

APPL-NO: 8/ 476018
DATE FILED: June 7, 1995

IN: Zhou; Xiaohuai, Muzyczka; Nicholas, Zolotukhin; Sergei, Ni; Tiehua

AB: A method for in vitro packaging of adeno-associated viral particles is described.
The procedure involves the preparation of cell-free extracts containing all the essential
components for packaging. Homogeneous purified substrate DNA for packaging may be prepared
separately. The in vitro packaged AAV particles are useful in transduction of mammalian

cells and for gene therapy in animals. In one described method, the DNA packaged into AAV
particles is not limited by the size constraints characteristic of in vivo packaged AAV
particles.

L6: Entry 15 of 33

File: USPT

Nov 18, 1997

DOCUMENT-IDENTIFIER: US 5688675 A
TITLE: In vitro packaging of adeno-associated virus DNA

BSPR:
The use of AAV as a viral transduction vector was first demonstrated by Hermonat and Muzyczka
(Proc. Natl Acad. Sci. 81:6466-6470 1984). The AAV capsid gene was deleted between map positions
52 and 92 to make the vector dl52-91, and the bacterial neomycin resistance gene under the
control of the SV40 early promoter was inserted. A dl52-91/neo virus stock was obtained by
transfecting the recombinant plasmid into human cells that had been infected with adenovirus. The
missing capsid proteins were supplied by co-transfecting with a plasmid containing wild type cap
genes. This approach generated dl51-91/neo virus stocks that contained up to 10.sup.6 infectious
units/ml (Hermonat et al. 1984 J. Virol., 51:329-333). The transduction frequency of these stocks
was approximately the same as the integration frequency for wild type virus, 0.5%-5.0% (Laughlin
et al. 1986 J. Virol. 60:515-524 (1986); Handa et al. 1977 Virology 82:84-92). Other AAV vectors
containing the AAV TR sequences and varying amounts of non-repeated AAV sequences have been
demonstrated to be capable of efficiently transducing foreign DNA into human cells (McLaughlin et
al. 1988 J. Virol. 62:1963-1973; Samulski et al. 1987 J. Virol. 61:3096-3101; Samulski et al.
1989 J. Virol. 63:3822-3828).

16. Document ID: US 5677158 A

L6: Entry 16 of 33

File: USPT

Oct 14, 1997

US-PAT-NO: 5677158
DOCUMENT-IDENTIFIER: US 5677158 A
TITLE: In vitro packaging of adeno-associated virus DNA
DATE-ISSUED: October 14, 1997

US-CL-CURRENT: 435/457; 435/235.1, 435/320.1

APPL-NO: 8/ 481603
DATE FILED: June 7, 1995

IN: Zhou; Xiaohuai, Muzyczka; Nicholas, Zolotukhin; Sergei, Ni; Tiehua

AB: A method for in vitro packaging of adeno-associated vital particles is described.
The procedure involves the preparation of cell-free extracts containing all the essential
components for packaging. Homogeneous purified substrate DNA for packaging may be prepared

separately. The in vitro packaged AAV particles are useful in transduction of mammalian
cells and for gene therapy in animals. In one described method, the DNA packaged into AAV
particles is not limited by the size constraints characteristic of in vivo packaged AAV
particles.

L6: Entry 16 of 33

File: USPT

Oct 14, 1997

DOCUMENT-IDENTIFIER: US 5677158 A
TITLE: In vitro packaging of adeno-associated virus DNA

BSPR:
The use of AAV as a viral transduction vector was first demonstrated by Hermonat and Muzyczka
(Proc. Natl Acad. Sci. 81:6466-6470 1984). The AAV capsid gene was deleted between map positions
52 and 92 to make the vector dl52-91, and the bacterial neomycin resistance gene under the
control of the SV40 early promoter was inserted. A dl52-91/neo virus stock was obtained by
transfecting the recombinant plasmid into human cells that had been infected with adenovirus. The
missing capsid proteins were supplied by co-transfecting with a plasmid containing wild type cap
genes. This approach generated dl51-91/neo virus stocks that contained up to 10.sup.6 infectious
units/ml (Hermonat et al. 1984 J. Virol., 51:329-333). The transduction frequency of these stocks
was approximately the same as the integration frequency for wild type virus, 0.5%-5.0% (Laughlin
et al. 1986 J. Virol. 60:515-524 (1986); Handa et al. 1977 Virology 82:84-92). Other AAV vectors
containing the AAV TR sequences and varying amounts of non-repeated AAV sequences have been
demonstrated to be capable of efficiently transducing foreign DNA into human cells (McLaughlin et
al. 1988 J. Virol. 62:1963-1973; Samulski et al. 1987 J. Virol. 61:3096-3101; Samulski et al.
1989 J. Virol. 63:3822-3828).

17. Document ID: US 5580766 A

L6: Entry 17 of 33

File: USPT

Dec 3, 1996

US-PAT-NO: 5580766
DOCUMENT-IDENTIFIER: US 5580766 A
TITLE: Retroviral vector particles for transducing non-proliferating cells
DATE-ISSUED: December 3, 1996

US-CL-CURRENT: 435/456; 435/235.1, 435/320.1, 435/325, 435/357, 435/69.1, 536/23.1, 536/23.4,
536/23.72, 536/24.1

APPL-NO: 8/ 181335
DATE FILED: January 14, 1994

IN: Mason; James M., Kennedy; Scott P., Fidel; Seth A.

AB: Retroviral vector particles are provided which contain: 1) oncoretroviral gag,
pol, and env proteins, including an oncoretroviral gag capsid protein

which has been mutated
so as to contain a nuclear localization signal (NLS) sequence; and 2) at least one exogenous
gene. The particles can be used to transduce non-proliferating cells, including stem cells
and neurons. The presence of the NLS sequence allows the at least one exogenous gene to
enter into the nucleus of a target cell, thus allowing integration of the gene into the
genome of the target cell.

L6: Entry 17 of 33

File: USPT

Dec 3, 1996

DOCUMENT-IDENTIFIER: US 5580766 A
TITLE: Retroviral vector particles for transducing non-proliferating cells

BSPR:
Preferred mutated forms of the MoMLV gag capsid protein which include the SV40 NLSs of SEQ. ID
NO:1 and SEQ. ID NO:4 are shown in SEQ. ID NO:5 and SEQ. ID NO:6, respectively.

18. Document ID: US 5508186 A

L6: Entry 18 of 33

File: USPT

Apr 16, 1996

US-PAT-NO: 5508186
DOCUMENT-IDENTIFIER: US 5508186 A
TITLE: B19 parvovirus capsids
DATE-ISSUED: April 16, 1996

US-CL-CURRENT: 435/235.1; 424/233.1, 435/236, 435/5

APPL-NO: 7/ 612672
DATE FILED: November 14, 1990

PARENT-CASE:
BACKGROUND OF THE INVENTION This application is a continuation-in-part of application Ser. No.
07/270,098 filed on Nov. 14, 1988, now abandoned, which is hereby incorporated in its entirety by
reference.

IN: Young; Neal S., Kajigaya; Sachiko, Shimada; Takashi

AB: The present invention relates to a method of producing non-infections parvovirus
capsids and to diagnostic assays and vaccines utilizing same. The invention further relates
to recombinant baculoviruses encoding parvovirus structural proteins and host cells infected
therewith. The invention also relates to a method of packaging and delivering genetic
information utilizing the noninfectious capsids.

L6: Entry 18 of 33

File: USPT

Apr 16, 1996

DOCUMENT-IDENTIFIER: US 5508186 A
TITLE: B19 parvovirus capsids

DEPR:
In a most preferred embodiment, CHO cells deficient in dihydrofolate reductase (DHFR) are
cotransfected with: i) a recombinant DNA molecule comprising an expression vector and a DNA
sequence encoding the two B19 parvovirus capsid proteins driven by the strong single B19
promoter, and ii) a human DHFR minigene driven by the SV40 early promoter enhancer unit.
Transformants bearing the DHFR+ phenotype are selected by growing the cells in a medium lacking
nucleosides; colonies are screened by RNA Northern analysis for expression of B19 genes.
Coamplification of the integrated B19 capsid-encoding sequence and the DHFR sequence can be
accomplished by treating the cells with increasing concentrations of methotrexate;
coamplification results in detectable levels of protein expression.

19. Document ID: US 5378806 A

L6: Entry 19 of 33

File: USPT

Jan 3, 1995

US-PAT-NO: 5378806
DOCUMENT-IDENTIFIER: US 5378806 A
TITLE: Fusion protein produced by retrovirus-mediated secretion
DATE-ISSUED: January 3, 1995

US-CL-CURRENT: 530/350; 435/69.7, 530/412, 536/23.4

APPL-NO: 7/ 881585
DATE FILED: May 12, 1992

PARENT-CASE:
This is a divisional of copending application Ser. No. 522,428, now U.S. Pat. No. 5,175,099,
filed on May 11, 1990 which is a continuation-in-part of U.S. Ser. No. 353,293 filed May 17, 1989
abandoned.

IN: Willis; John W.

AB: The present invention is directed to replicable expression vectors for producing
fusion proteins which are secreted in membraneous particles budded from the cell membrane.
In particular these vectors express a hybrid gene product composed of a modified retrovirus
gag gene fused to a heterologous gene, or any part thereof, wherein the gag gene
modification is sufficient to enable a cell to produce the hybrid gene product in a
membraneous particle by budding from the cell membrane into the culture medium or
extracellular space, a process known as retrovirus-mediated secretion. The minimum gag
sequences needed to obtain particle formation are described. The invention also provides
hosts containing the expression vectors, and the fusion proteins produced by the vectors.
Further the invention provides the membraneous particles produced by retrovirus-mediated
secretion and uses of these particles for protein purification and in therapeutics.

L6: Entry 19 of 33

File: USPT

Jan 3, 1995

DOCUMENT-IDENTIFIER: US 5378806 A
TITLE: Fusion protein produced by retrovirus-mediated secretion

DEPV:
i) p.DELTA.SV.GAGX. This plasmid contains DNA fragments from three sources: the RSV genome, the
SV40 genome, and the bacterial plasmid, pAT153. The RSV Sac-HindIII fragments contains the gag
gene and was modified by inserting an XbaI linker (5'-CTCTAGAG-3') into the HpaI site (nt2731) by
means of blunt-end ligation. The SacI end was made blunt using the Klenow fragment of E. coli DNA
polymerase. The HindIII end was not modified. The SV40 fragment was obtained from d12005, an SV40
mutant lacking approximately 230 bp of the T-antigen intron (Sleigh et al. 1978, Cell 14: 79-88).
This viable mutant produces fully functional T-antigen. The fragment used here extends from the
BamHI site (wild-type SV40 nt 2533) to the HpaII site (nt346) and includes the early region,
replication origin, and late promoter; the portion of the SV40 genome which codes for capsid
proteins is missing. The HpaII end was made blunt using Klenow and a ClaI linker was attached
using T4 DNA polymerase. The BamHI end was modified with a polylinker resulting in the sequence
of sites: BamHI-XbaI-BamHI-ClaI. The portion of pAT153 used lacks the 6 bp region between the
ClaI and HindIII sites; the EcoRI site was removed by digestion with EcoRI, filling with Klenow,
and ligating. Several subcloning steps were required to assemble p SV.GAGX and the final product
is linked as follows: The destroyed HpaII end near the SV40 late promoter is joined to the
destroyed SacI end of the RSV fragment by means of the ClaI linker. The 3'-end of the RSV
fragment is joined to pAT153 via their intact HindIII sites. The intact ClaI end of the pAT153
sequence is joined to SV40 fragment via the ClaI site of the polylinker, BamHI-XbaI-BamHI-ClaI.

20. Document ID: US 5213796 A

L6: Entry 20 of 33

File: USPT

May 25, 1993

US-PAT-NO: 5213796
DOCUMENT-IDENTIFIER: US 5213796 A
TITLE: Assay for polyomavirus in humans and uses thereof
DATE-ISSUED: May 25, 1993

US-CL-CURRENT: 424/204.1; 435/5

APPL-NO: 7/ 695647
DATE FILED: May 6, 1991

IN: Garcea; Robert L., Bergsagel; Daniel J.

AB: Methods for detecting the propensity for an individual to be affected by a
polyomavirus are disclosed. The methods include an assay wherein a biological specimen from
a female is contacted with at least one probe capable of determining whether the female has
been exposed to a polyomavirus. A method for prophylactically treating the female is also
described.

L6: Entry 20 of 33

File: USPT

May 25, 1993

DOCUMENT-IDENTIFIER: US 5213796 A
TITLE: Assay for polyomavirus in humans and uses thereof

BSPR:
One can prophylactically treat a seronegative woman prior to the onstart of pregnancy by
administering a vaccine containing a polyoma antigen. In one embodiment this would be by using
capsid protein to SV40, capsid protein to BKV and/or capsid protein to JCV in order to develop
antibodies for the virus(es) which the female is seronegative to.

DEPR:
Choroid plexus tumors occur in humans almost exclusively within the first year of life. However,
this tumor is relatively rare and represents only about 3% of all pediatric brain tumors.
One-half are diagnosed before age 1 and 80% by age 5. They are slow growing tumors and their
pathology varies. However, the earlier it is possible to discover the tumor, the greater the
treatment choices. Because of its rarity, formalin-fixed, paraffin-embedded tissue sections of CP
neoplasms from the archives of the Children's Hospital, Boston, Mass., Pathology Department were
examined. The polymerase chain reaction technique (PCR) was used to amplify a specific segment of
the viral genome. The initial investigation was whether BKV and/or JCV might be present in these
tumors. Specimens were examined for the presence of T-antigen sequences for both BKV and JCV.
Instead of finding BKV or JCV, we surprisingly found that there was a DNA sequence present which
corresponds to an SV40-like virus. As used herein, the term "SV40-like" virus includes the SV40
virus, a fragment of the SV40 virus that retains SV40 properties when tested in vitro, a virus
that has a similar genomic organization to SV40 with 2 early and 3 late proteins, and a virus
capsid which is non-envelope of T-7 symmetry comprised of 72 capsomeres. As the term is used
herein viruses with changes in the promoter region are considered SV40-like. Preferably, the
SV40-like virus corresponds to at least 80% of the nucleotide sequence of the SV40 virus encoding
the large T antigen, more preferably, it corresponds to at least about 85% of such nucleotide
sequence and still more preferably, it corresponds to at least about 90% of such nucleotide
sequence.

21. Document ID: US 5198536 A

L6: Entry 21 of 33

File: USPT

Mar 30, 1993

US-PAT-NO: 5198536
DOCUMENT-IDENTIFIER: US 5198536 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAs

containing nucleotide
sequences coding for these peptides
DATE-ISSUED; March 30, 1993

US-CL-CURRENT: 530/405; 424/186.1, 424/196.11, 424/217.1, 435/320.1, 530/324, 530/325, 530/326, 530/327, 530/350, 530/387.9, 530/388.3, 530/403, 530/404, 930/220

APPL-NO: 7/ 730066
DATE FILED: July 15, 1991

PARENT-CASE:
This is a division of application Ser. No. 07/538,668, filed on Jun. 15, 1990, now U.S. Pat. No. 5,061,623, which is a division of 07/222,392, filed Jul. 21, 1988, now U.S. Pat. No. 4,940,781, which is a continuation of 07/084,932, filed Aug. 13, 1987, now abandoned; which was a division of 06/634,881 filed Jul. 27, 1984, now U.S. Pat. No. 4,694,072.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	82 20115	November 30, 1982
FR	83 10778	June 29, 1983

IN: Girard; Marc, Van Der Werf; Sylvie

AB: The invention relates to a DNA fragment containing at the most 315 pairs of nucleotides coding for a peptide which can be recognized by antibodies acting both against the "C" and "D" particles of the same poliovirus and against the VP-1 structural polypeptide of the capsid of this poliovirus. This peptide contains in particular the following sequence:, Asp Asn Pro Ala Ser thr Thr Asn Lys Asp Lys Leu.

L6: Entry 21 of 33
File: USPT
Mar 30, 1993

DOCUMENT-IDENTIFIER: US 5198536 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAs containing nucleotide sequences coding for these peptides

DEPR:
They are particularly suitable when the SV40 is used as vector. In this case, the late viral promoter is used and the sequence of the poliovirus is inserted in place of all or part of the region coding for the late proteins of SV40 (VP1 or VP2). In this way substituted DNAs of SV40 are constructed in which the sequences coding for the capsid proteins of this virus are replaced by the sequence coding for the immunogenic peptide. Thus the insertion of said sequence, if need be through suitable linkers in place of the late fragment HaeII-PstI of SV40 (nucleotides from 767 to 1923), or of a portion of this fragment, results in the creation of a chimeric gene possessing a sequence coding for an immunogenic peptide inducing in vivo antibodies active with respect to poliovirus directly downstream of the N terminal portion of the protein VP2 of SV40.

22. Document ID: US 5175099 A

L6: Entry 22 of 33
File: USPT
Dec 29, 1992

US-PAT-NO: 5175099
DOCUMENT-IDENTIFIER: US 5175099 A
TITLE: Retrovirus-mediated secretion of recombinant products
DATE-ISSUED: December 29, 1992

US-CL-CURRENT: 435/69.7; 435/252.3, 435/320.1, 530/350, 536/23.72

APPL-NO: 7/ 522428
DATE FILED: May 11, 1990

PARENT-CASE:
This application is a continuation-in-part of U.S. Ser. No. 353,293 filed May 17, 1989, now abandoned.

IN: Wills; John W.

AB: The present invention is directed to replicable expression vectors for producing fusion proteins which are secreted in membraneous particles budded from the cell membrane.
In particular these vectors express a hybrid gene product composed of a modified retrovirus gag gene fused to a heterologous gene, or any part thereof, wherein the gag gene modification is sufficient to enable a cell to produce the hybrid gene product in a membraneous particle by budding from the cell membrane into the culture medium or extracellular space, a process known as retrovirus-mediated secretion. The minimum gag sequences needed to obtain particle formation are described. The invention also provides hosts containing the expression vectors, and the fusion proteins produced by the vectors.
Further the invention provides the membraneous particles produced by retrovirus-mediated secretion and uses of these particles for protein purification and in therapeutics.

L6: Entry 22 of 33
File: USPT
Dec 29, 1992

DOCUMENT-IDENTIFIER: US 5175099 A
TITLE: Retrovirus-mediated secretion of recombinant products

DEPR:
This plasmid contains DNA fragments from three sources: the RSV genome, the SV40 genome, and the bacterial plasmid, pAT153. The RSV Sac-HindIII fragments contains the gag gene and was modified by inserting an XbaI linker (5'-CTCTAGAG-3') into the HpaI site (nt2731) by means of blunt-end ligation. The SacI end was made blunt using the Klenow fragment of E.coli DNA polymerase. The HindIII end was not modified. The SV40 fragment was obtained from d12005, an SV40 mutant lacking approximately 230 bp of the T-antigen intron (Sleigh et al. 1978, Cell 14: 79-88). This viable mutant produces fully functional T-antigen. The fragment used here extends from the BamHI site

(wild-type SV40 nt 2533) to the HpaII site (nt346) and includes the early region, replication origin, and late promoter; the portion of the SV40 genome which codes for capsid proteins is missing. The HpaII end was made blunt using Klenow and a ClaI linker was attached using T4 DNA polymerase. The BamHI end was modified with a polylinker resulting in the sequence of sites: BamHI-XbaI -BamHI-ClaI. The portion of pAT153 used lacks the 6 bp region between the ClaI and HindIII sites; the EcoRI site was removed by digestion with EcoRI, filling with Klenow, and ligating. Several subcloning steps were required to assemble p SV.GAGX and the final product is linked as follows: The destroyed HpaII end near the SV40 late promoter is joined to the destroyed SacI end of the RSV fragment by means of the ClaI linker. The 3'-end of the RSV fragment is joined to pAT153 via their intact HindIII sites. The intact ClaI end of the pAT153 sequence is joined to SV40 fragment via the ClaI site of the polylinker, BamHI-XbaI -BamHI-ClaI.

23. Document ID: US 5118627 A

L6: Entry 23 of 33

File: USPT

Jun 2, 1992

US-PAT-NO: 5118627
DOCUMENT-IDENTIFIER: US 5118627 A
TITLE: Papova virus construction
DATE-ISSUED: June 2, 1992

US-CL-CURRENT: 435/466; 435/320.1, 435/69.3

APPL-NO: 6/ 584132
DATE FILED: February 27, 1984

IN: Browne; Jeffrey K.

AB: A microbial shuttle vector is disclosed which is independently replicative in bacterial cells and mammalian cells and includes in its DNA sequence bacterial plasmid sequences allowing selection and replication in bacterial cells, an SV40 viral origin of replication, and either an SV40 functional "early gene" promoter and functional "early gene" terminator or an SV40 functional "late gene" promoter and functional "late gene" terminator, the vector having a unique restriction endonuclease enzyme recognition site between the promoter and terminator for insertion of an exogenous gene. The presence of restriction endonuclease enzyme recognition sites facilitative of insertion of a viral functional "late gene" into the "early gene" promoter/terminator vector in a single step allows for conversion of the shuttle vector into a lytic vector of an exogenous gene. The presence of restriction endonuclease enzyme recognition sites facilitative of insertion of a viral functional "late gene" into the "late gene" promoter/terminator vector in a single step allows for conversion of the shuttle vector into a lytic vector.

L6: Entry 23 of 33

File: USPT

DOCUMENT-IDENTIFIER: US 5118627 A
TITLE: Papova virus construction

BSPR:
An SV40-based viral vector may be constructed by replacing SV40 early gene regions or SV40 late gene regions with an exogenous gene sequence. If an exogenous gene is inserted to replace a deleted early viral gene DNA sequence coding for T antigen, the recombinant virus must be propagated in the presence of SV40 T antigen, e.g., supplied by simian COS-1 cells (ATCC CRL1650) or co-infection with a helper virus. Alternatively, if late viral gene DNA is excised from SV40 to permit insertion of the exogenous gene coding sequence, the early T antigen gene is present but the DNA sequences coding for expression of essential capsid proteins is absent. Therefore, these recombinant viruses must infect a host cell in concert with a "helper" virus which supplies the missing proteins. Early gene replacement viral vectors, which are easily propagated in COS cells which supply SV40 T antigen, are technically more adaptable to experimental manipulation than late gene replacement viral vectors, which require co-infection with a helper virus.

BSPR:
A disadvantage incurred in using the SV40 viral vectors for expression of exogenous genes in mammalian cells, resides in inherent limitations on the size of the viral vector. It has been concluded that the icosohedral symmetry of the SV40 virion imposes restrictions on the size of the DNA that could be encapsulated by its capsid proteins. Because the expression of the exogenous gene typically requires propagation of the recombinant molecules, the addition of exogenous genes without removal of viral sequences, or the insertion of genes larger than the viral sequences removed is precluded by the packaging constraints of SV40 [see, Liu, C., et al., "Expression of HE Surface Antigen Using Lytic and Non-Lytic SV40 Based Vectors in Eukaryotic Viral Vectors", Y. Gluzman, ed., Cold Spring Harbor Laboratory, Cold Spring, N.Y., 1982, pages 55-60; and Liu, et al., DNA, 1, pages 213-221 (1982)].

BSPR:
In Liu, DNA, 1, supra, an SV40 vector for the direct expression of exogenous genes was constructed by eliminating SV40 genome sequences between HindIII (1493) [6 nucleotides 5' to the initiation codon for the gene coding for the major SV40 late protein, VP1, which is essential in capsid formation] and BamHI (2533) [50 nucleotides 5' to the termination codon for that gene]. A unique EcoRI restriction endonuclease enzyme recognition site was introduced into the SV40 genome at the HindIII terminus to allow the SV40 fragment to be cloned into pBR322 and amplified. A BamHI/EcoRI exogenous gene sequence, e.g., HBsAg, is inserted into the SV40 fragment in place of the deleted VP1 sequence and the SV40-HBsAg fragment cloned into a pBR322 derivative and amplified. Cleavage with BamHI and self-ligation results in a recombinant virus plasmid vector, therefore, lacking only the coding region of VP1 and containing the whole protein coding region for T antigen. When the recombinant SV40/hepatitis B virus DNA was introduced into permissive monkey cells by DNA transfection in the presence of helper virus (tsA28), which supplies the capsid protein normally expressed by the deleted VP1, HBsAg was

synthesized at a level comparable
to that of VP1.

BSPR:
In formation of a late replacement vector, the exogenous influenza virus hemaglutinin gene was
inserted between the HpaII (346) and BamHI (2533) sites of the SV40 genome replacing the deleted
late gene region. Thereafter, the recombinant viral genome SV40-HA was cloned into the BamHI site
of an E.coli pBR322 derivative plasmid and propagated in E.coli. The recombinant SV40-HA genome
was excised from the plasmid by BamHI digestion, purified and self-ligated to form the vector
which contained the SV40 origin of DNA replication and an intact set of early genes including an
intact copy of the gene coding for SV40 large T antigen. Presence of the early coding region and
viral origin of replication permitted replication of the vector DNA in permissive simian cells
and complementation by helper virus supplied SV40 capsid proteins for the assembly of infectious
virions.

24. Document ID: US 5061623 A

L6: Entry 24 of 33
File: USPT
Oct 29, 1991

US-PAT-NO: 5061623
DOCUMENT-IDENTIFIER: US 5061623 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAs containing nucleotide
sequences coding for these peptides
DATE-ISSUED: October 29, 1991

US-CL-CURRENT: 435/69.3; 435/252.3, 435/252.33, 435/320.1, 435/69.1, 536/23.72

DISCLAIMER DATE: 20071106
APPL-NO: 7/ 538668
DATE FILED: June 15, 1990

PARENT-CASE:
This is a division of application Ser. No. 07/222,392, filed on July 21, 1988 now U.S. Pat. No.
4,968,627 which is a continuation of Ser. No. 07/84,932, filed Aug. 13, 1987; now abandonded,
which is a divisional of Ser. No. 06/634,881, filed July 27, 1984, now U.S. Pat. No. 4,694,072.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	82 20115	November 30, 1982
FR	83 10778	June 29, 1983

IN: Girard; Marc, Van Der Werf; Sylvie

AB: The invention relates to a DNA fragment containing at the most 315 pairs of
nucleotides coding for a peptide which can be recognized by antibodies acting both against
the "C" and "D" particles of the same poliovirus and against the VP-1 structural polypeptide
of the capsid of this poliovirus. This peptide contains in particular the following
sequence: Asp Asn Pro Ala Ser Thr Asn Lys Asp Lys Leu.

L6: Entry 24 of 33
File: USPT
Oct 29, 1991

DOCUMENT-IDENTIFIER: US 5061623 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAs containing nucleotide
sequences coding for these peptides

DEPR:
They are particularly suitable when the SV40 is used as vector. In this case, the late viral
promoter is used and the sequence of the poliovirus is inserted in place of all or part of the
region coding for the late proteins of SV40 (VP1 or VP2). In this way substituted DNAs of SV40
are constructed in which the sequences coding for the capsid proteins of this virus are replaced
by the sequence coding for the immunogenic peptide. Thus the insertion of said sequence, if need
be through suitable linkers in place of the late fragment HaeII-PstI of SV40 (nucleotides from
767 to 1923), or of a portion of this fragment, results in the creation of a chimeric gene
possessing a sequence coding for an immunogenic peptide inducing in vivo antibodies active with
respect to poliovirus directly downstream of the N terminal portion of the protein VP2 of SV40.

25. Document ID: US 5041376 A

L6: Entry 25 of 33
File: USPT
Aug 20, 1991

US-PAT-NO: 5041376
DOCUMENT-IDENTIFIER: US 5041376 A
TITLE: Method for identifying or shielding functional sites or epitopes of proteins that enter
the exocytotic pathway of eukaryotic cells, the mutant proteins so produced and genes encoding
said mutant proteins
DATE-ISSUED: August 20, 1991

US-CL-CURRENT: 435/6; 435/466, 435/7.21, 435/7.6

APPL-NO: 7/ 282165
DATE FILED: December 9, 1988

IN: Gething; Mary J., Sambrook; Joseph F., Gallagher; Patricia

AB: The present invention relates to a method for identifying or shielding functional
sites or epitopes of proteins that enter the exocytotic pathway of eukaryotic cells
(transportable proteins) by the addition of supernumerary N-linked oligosaccharide side
chains at chosen sites on the surface thereof using oligonucleotide mutagenesis. The present
invention also relates to mutant transportable proteins having supernumerary N-linked

oligosaccharide side chains which shield functional sites or epitopes; and genes which
encode the same.

L6: Entry 25 of 33
File: USPT
Aug 20, 1991

DOCUMENT-IDENTIFIER: US 5041376 A
TITLE: Method for identifying or shielding functional sites or epitopes of proteins that enter
the exocytotic pathway of eukaryotic cells, the mutant proteins so produced and genes encoding
said mutant proteins

DEPR:
Vector SVEXHA-A.sup.- was constructed to express the X-31 HA ectodomain. This vector closely
resembles SVEHA20-A.sup.- which has been used to express the ectodomain of the HA gene from the
A/Japan/305/57 strain of influenza virus (Gething, M. J. et al, Nature, 300:598-603 (1982)).
Vector SVEXHA-A.sup.- contains the ClaI-BamHI restriction fragment encoding the X-31 HA
ectodomain inserted between the HpaII (nucleotide 346) and BamHI (nucleotide 2533) restriction
sites of SV40 DNA, so that the HA sequences replace the late region of the SV40 genome which
encodes the capsid proteins. For amplification and manipulation of the DNA sequences, the SV40
genome was inserted through the unique KpnI site in the SV40 sequence into plasmid pKSB (Doyle,
C. et al, J. Cell Biol. 100:704-714 (1985)).

26. Document ID: US 5024939 A

L6: Entry 26 of 33
File: USPT
Jun 18, 1991

US-PAT-NO: 5024939
DOCUMENT-IDENTIFIER: US 5024939 A
TITLE: Transient expression system for producing recombinant protein
DATE-ISSUED: June 18, 1991

US-CL-CURRENT: 435/69.1; 435/461, 435/466

APPL-NO: 7/ 101712
DATE FILED: September 25, 1987

PARENT-CASE:
This is a Continuation-in-Part of U.S. Ser. No. 07/071,674, filed July 9, 1987, now abandoned,
which is a Continuation-in-Part of U.S. Ser. No. 06/907,185 filed Sept. 12, 1986, now abandoned.

IN: Gorman; Cornelia M.

AB: A method is described for transient production of a desired heterologous protein
comprising: transfecting a eukaryotic host cell with a vector producing a trans-activating
protein; transfecting the eukaryotic host cell with an expression vector comprising a
stabilizing sequence downstream of a promoter and upstream of a DNA encoding the desired
heterologous protein and a polyadenylation sequence downstream of which is a transcription
terminatein site; culturing the transfected eukaryotic host cell under conditions favorable
for production of said desired heterologous protein; and, recovering the desired protein in
useful amounts within about one day to about fourteen days of transfection.

L6: Entry 26 of 33
File: USPT
Jun 18, 1991

DOCUMENT-IDENTIFIER: US 5024939 A
TITLE: Transient expression system for producing recombinant protein

BSPR:
In an attempt to establish the physiological role that RNA splicing plays in gene expression,
Hamer, D. H. and Leder, P., Cell 18, 1299-1302 (1979) manipulated the location and/or presence of
a splice site in SV40 recombinants transfected into monkey cells. Hamer and Leder, supra, used
one splice site located within the gene encoding the desired protein or used two splice site
sequences, one located 5' to and the second within the gene encoding the desired protein. They
found that RNA were produced transiently by all of the viruses that retain at least one
functional splice junction. They concluded that splicing is a prerequisite for stable RNA
formation. Confirming that result, Gruss, P. et al. PNAS (USA), 76 4317-4321 (1979) found that
construction of an SV40 mutant lacking an intervening sequence made no detectable capsid protein.
These two papers suggest that RNA splicing may be important in a recombinant milieu. However,
other studies abandoned splicing to express proteins using only 5' control signals such as
enhancers, and promoters and 3' polyadenylation sites. In fact, recent work by Reddy, U. B. et
al., Transcriptional Control Mechanisms, J. Cell. Biochem. Suppl. 10D, 154 (1986), found that the
inclusion of introns in an expression vector actually reduced the amount of the desired protein
expressed.

27. Document ID: US 4968627 A

L6: Entry 27 of 33
File: USPT
Nov 6, 1990

US-PAT-NO: 4968627
DOCUMENT-IDENTIFIER: US 4968627 A
TITLE: DNA fragments coding an immunogen peptide liable of inducing in vivo synthesis of
anti-poliovirus antibodies
DATE-ISSUED: November 6, 1990

US-CL-CURRENT: 435/320.1; 424/185.1, 424/217.1, 435/91.41, 536/23.72

APPL-NO: 6/ 886754
DATE FILED: July 15, 1986

PARENT-CASE:
This application is a continuation of application Ser. No. 464,175, filed 2/7/83, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
FR
82 02013
February 8, 1982

IN: Girard; Marc, van der Werf; Sylvie

AB: DNA fragment capable of coding for an immunogenic peptide capable of inducing in
vivo antibody reacting with anti-poliovirus. It possesses up to the order of 1.2 kilobase
pairs and contains a nucleotide sequence coding for the poliovirus VP1 protein.

L6: Entry 27 of 33
File: USPT
Nov 6, 1990

DOCUMENT-IDENTIFIER: US 4968627 A
TITLE: DNA fragments coding an immunogen peptide liable of inducing in vivo synthesis of
anti-poliovirus antibodies

DEPR:
It is particularly the case of the use of the virus SV40 as vector. In this case, the late viral
promoter is used and the VP1 fragment of the poliovirus is inserted in the place of all or part
of the region coding for the tardive proteins of SV40 (VP1 or VP2). In this way substituted SV40
DNas are constructed in which the sequences coding for the capsid proteins of this virus are
replaced by the sequence coding for the VP1 protein of the poliovirus. Thus, the insertion of the
fragment HaeII-PstI of poliovirus described in paragraph 3 above, in place of the tardive
fragment Hae II-PstI of SV40 (nucleotides from 767 to 1923) results, after phase restoration of
the two sequences at the level of the HaeII site, in creating a chimerical gene possessing the
VP1 sequence of the poliovirus directly linked behind and to the N terminal portion of the
sequence coding for the VP2 protein of SV40.

DEPR:
Numerous other constructions are possible, for example by insertion of the PstI fragment of the
poliovirus (1.17 kb fragment) at the PstI site (nucleotide 1923) of SV40 or by insertion of the
fragment HaeII-PstI in place of the sequences AccI-BamHI(1563 to 2468) of the SV40. All the
chimerical SV40's so constituted are defective. They can only grow in the presence of an
assistant virus (for example a ts A30 or ts A58 type early mutant) which contributes to the
production of the capsid proteins of SV40.

28. Document ID: US 4940781 A

L6: Entry 28 of 33
File: USPT
Jul 10, 1990

US-PAT-NO: 4940781
DOCUMENT-IDENTIFIER: US 4940781 A
TITLE: Peptides comprising an immunogenic side of poliovirus and DNAs containing nucleotide
sequences coding for these peptides
DATE-ISSUED: July 10, 1990

US-CL-CURRENT: 530/350; 530/324, 530/325, 530/326, 530/327

DISCLAIMER DATE: 20050915
APPL-NO: 7/222392
DATE FILED: July 21, 1988

PARENT-CASE:
This application is a continuation of application Ser. No. 084,932, filed on Aug. 13, 1987, now
abandoned, which is a division of Ser. No. 634,881 filed July 27, 1984, now U.S. Pat. No.
4,694,072.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
FR
82 20115
November 30, 1982
FR
83 10778
June 29, 1983

IN: Girard; Marc, Van Der Werf; Sylvie

AB: Peptides which can be recognized by antibodies acting both against the "C" and
"D" particles of the same poliovirus and against the VP-1 structural polypeptides of this
capsid of the poliovirus. These peptides comprise the amino acid sequence: Asp Asn Pro Ala
Ser Thr Thr Asn Lys Asp Lys Leu; and one or more additional amino acids in a specified
sequence.

L6: Entry 28 of 33
File: USPT
Jul 10, 1990

DOCUMENT-IDENTIFIER: US 4940781 A
TITLE: Peptides comprising an immunogenic side of poliovirus and DNAs containing nucleotide
sequences coding for these peptides

DEPR:
They are particularly suitable when the SV40 is used as vector. In this case, the late viral
promoter is used and the sequence of the poliovirus is inserted in place of all or part of the
region coding for the late proteins of SV40 (VP1 or VP2). In this way substituted DNAs of SV40
are constructed in which the sequences coding for the capsid proteins of this virus are replaced
by the sequence coding for the immunogenic peptide. Thus the insertion of said sequence, if need
be through suitable linkers in place of the late fragment HaeII-PstI of SV40 (nucleotides from
767 to 1923), or of a portion of this fragment, results in the creation of a chimeric gene
possessing a sequence coding for an immunogenic peptide inducing in vivo antibodies active with
respect to poliovirus directly downstream of the N terminal portion of the protein VP2 of SV40.

29. Document ID: US 4853324 A

L6: Entry 29 of 33

File: USPT

Aug 1, 1989

US-PAT-NO: 4853324
DOCUMENT-IDENTIFIER: US 4853324 A
TITLE: Liver assist device employing transformed cell lines
DATE-ISSUED: August 1, 1989

US-CL-CURRENT: 435/375; 435/297.2, 435/320.1, 435/401

APPL-NO: 6/ 931249
DATE FILED: November 17, 1986

PARENT-CASE:
This is a division of application Ser. No. 803,564, now U.S. Pat. No. 4,675,002, filed on Dec. 2, 1985.

IN: Viles; Joseph M., Hart; Paul V.

AB: An improved extracorporeal liver assist device and method is provided which employs a blood perfusion membrane cultured with initially transformed hepatocytes until a confluent monolayer is developed, whereupon the hepatocytes are reverted to the somatic phenotype for perfusion purposes. Use of transformed hepatocytes permits serial subculturing to maintain a clinical supply of cells for the patient, while the in vitro proliferation characteristics and loss of contact inhibition of the transformed hepatocytes ensures rapid cell division and layer formation on the perfusion membranes. Virally transformed, temperature sensitive hepatocytes are preferred so that reversion of the cells can be accomplished by temperature change. The transformed hepatocytes may be cultured on the exterior surfaces of multiple capillary membrane cartridges, and subsequently reverted by elevating the temperature thereof. During perfusion, the patient's blood is passed through the lumen of the capillaries, and dissolved molecular species (e.g., bilirubin) diffuse through the membrane to be taken up and metabolized by the hepatocytes. Bathing solution is simultaneously passed around the exterior of the capillary tubes to remove metabolic wastes from the hepatocytes.

L6: Entry 29 of 33

File: USPT

Aug 1, 1989

DOCUMENT-IDENTIFIER: US 4853324 A
TITLE: Liver assist device employing transformed cell lines

DEPR:
While a wide variety of transformants can be employed to achieve transformation, it is preferred to make use of viral transforming agents in accordance with the present invention. The papovavirus group, and particularly SV40, is preferred as a transforming agent. Human cells are semipermissive of SV40 infection, that is, they can be infected and they support viral replication, but they do not all complete the lytic cycle. The survivors of the lytic cycle are transformed and exhibit the desired growth characteristics; however, they do continue to release SV40 virions after months of culture. SV40 has a much more restricted oncogenic potential than other papovaviruses. Considering the history of the exposure to SV40, it would seem probable that it is not oncogenic in humans, and indeed to date the only reported case of SV40 associated human disease is a single case of malignant melanoma. A wide variety of attenutated SV40 mutants are available, particularly group A mutants which are defective in early gene (A) function; they induce SV40 T antigen synthesis and stimulate the replication of host cell DNA, but fail to produce any viral DNA or capsid antigens under certain experimental conditions. These mutants in the (A) gene region produce a heat labile T antigen, necessary to maintain transformation, which ceases to function at elevated temperatures. Transformation by these temperature sensitive SV40 mutants is therefore reversible by simply increasing the temperature of the culture. When the temperature is elevated, the transformed cells ceases to produce SV40 viral DNA or SV40 capsids, lose their transformed characteristics, and revert to the original somatic phenotype.
Transformation with temperature sensitive SV40 thus permits switching from the transformed phenotype back to the somatic phenotype by elevating the temperature a few degrees; this then allows the utilization of the proliferation rate of the transformed state to grow rapidly large area confluent monolayers on a semipermeable membrane substrate, whereupon virus production can be stopped and reversion effected to the somatic phenotype for metabolic perfusions.

30. Document ID: US 4694072 A

L6: Entry 30 of 33

File: USPT

Sep 15, 1987

US-PAT-NO: 4694072
DOCUMENT-IDENTIFIER: US 4694072 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAS containing nucleotide sequences coding for these peptides
DATE-ISSUED: September 15, 1987

US-CL-CURRENT: 530/350; 530/324, 530/327, 930/220

APPL-NO: 6/ 634881
DATE FILED: July 27, 1984

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	82 20115	November 30, 1982
FR	83 10778	June 29, 1983

PCT-DATA:

APPL-NO
DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/FR83/00241
November 30, 1983
Jul 27, 1984
Jul 27, 1984

IN: Girard; Marc, van der Werf; Sylvie

AB: The invention relates to a DNA fragment containing at the most 315 parts of .
nucleotides coding for a peptide which can be recognized by antibodies acting both against
the "C" and "D" particles of the same poliovirus and against the VP-1 structural polypeptide
of the capsid of this poliovirus. This peptide contains in particular the following
sequence:, Asp Asn Pro Ala Ser Thr Thr Asn Lys Asp Lys Leu.

L6: Entry 30 of 33
File: USPT
Sep 15, 1987

DOCUMENT-IDENTIFIER: US 4694072 A
TITLE: Peptides comprising an immunogenic site of poliovirus and DNAS containing nucleotide
sequences coding for these peptides

DEPR:
They are particularly suitable when the SV40 is used as vector. In this case, the late viral
promoter is used and the sequence of the poliovirus is inserted in place of all or part of the
region coding for the late proteins of SV40 (VP1 or VP2). In this way substituted DNAs of SV40
are constructed in which the sequences coding for the capsid proteins of this virus are replaced
by the sequence coding for the immunogenic peptide. Thus the insertion of said sequence, if need
be through suitable linkers in place of the late fragment HaeII-PstI of SV40 (nucleotides from
767 to 1923), or of a portion of this fragment, results in the creation of a chimeric gene
possessing a sequence coding for an immunogenic peptide inducing in vivo antibodies active with
respect to poliovirus directly downstream of the N terminal portion of the protein VP2 of SV40.

31. Document ID: US 4675002 A

L6: Entry 31 of 33
File: USPT
Jun 23, 1987

US-PAT-NO: 4675002
DOCUMENT-IDENTIFIER: US 4675002 A
TITLE: Liver assist device employing transformed cell lines
DATE-ISSUED: June 23, 1987

US-CL-CURRENT: 604/6.06

APPL-NO: 6/ 803564

DATE FILED: December 2, 1985

IN: Viles; Joseph M., Hart; Paul V.

AB: An improved extracorporeal liver assist device and method is provided which
employs a blood perfusion membrane cultured with initially transformed hepatocytes until a
confluent monolayer is developed, whereupon the hepatocytes are reverted to the somatic
phenotype for perfusion purposes. Use of transformed hepatocytes permits serial subculturing
to maintain a clinical supply of cells for the patient, while the in vitro proliferation
characteristics and loss of contact inhibition of the transformed hepatocytes ensures rapid
cell division and layer formation on the perfusion membranes. Virally transformed,
temperature sensitive hepatocytes are preferred so that reversion of the cells can be
accomplished by temperature change. The transformed hepatocytes may be cultured on the
exterior surfaces of multiple capillary membrane cartridges, and subsequently reverted by
elevating the temperature thereof. During perfusion, the patient's blood is passed through
the lumen of the capillaries, and dissolved molecular species (e.g., bilirubin) diffuse
through the membrane to be taken up and metabolized by the hepatocytes. Bathing solution is
simultaneously passed around the exterior of the capillary tubes to remove metabolic wastes
from the hepatocytes.

L6: Entry 31 of 33
File: USPT
Jun 23, 1987

DOCUMENT-IDENTIFIER: US 4675002 A
TITLE: Liver assist device employing transformed cell lines

DEPR:
While a wide variety of transformants can be employed to achieve transformation, it is preferred
to make use of viral transforming agents in accordance with the present invention. The
papovavirus group, and particularly SV40, is preferred as a transforming agent. Human cells are
semipermissive of SV40 infection, that is, they can be infected and they support viral
replication, but they do not all complete the lytic cycle. The survivors of the lytic cycle are
transformed and exhibit the desired growth characteristics; however, they do continue to release
SV40 virions after months of culture. SV40 has a much more restricted oncogenic potential than
other papovaviruses. Considering the history of the exposure to SV40, it would seem probable that
it is not oncogenic in humans, and indeed to date the only reported case of SV40 associated human
disease is a single case of malignant melanoma. A wide variety of attenuated SV40 mutants are
available, particularly group A mutants which are defective in early gene (A) function; they
induce SV40 T antigen synthesis and stimulate the replication of host cell DNA, but fail to
produce any viral DNA or capsid antigens under certain experimental conditions. These mutants in
the (A) gene region produce a heat labile T antigen, necessary to maintain transformation, which
ceases to function at elevated temperatures. Transformation by these temperature sensitive SV40
mutants is therefore reversible by simply increasing the temperature of the culture. When the

temperature is elevated, the transformed cells cease to produce SV40 viral DNA or SV40 capsids,

lose their transformed characteristics, and revert to the original somatic phenotype.

Transformation with temperature sensitive SV40 thus permits switching from the transformed

phenotype back to the somatic phenotype by elevating the temperature a few degrees; this then

allows the utilization of the proliferation rate of the transformed state to grow rapidly large

area confluent monlayers on a semipermeable membrane substrate, whereupon virus production can be

stopped and reversion effected to the somatic phenotype for metabolic perfusions.